THE RELATIONSHIP OF CERTAIN ASPECTS

OF METABOLIC LEVEL

TO HIGH OXYGEN POISONING IN RATS

Milton Sharp Grossman

AM 1948 Gr c.1

# Boston University College of Liberal Arts Library

# BOSTON UNIVERSITY GRADUATE SCHOOL

#### Thesis

THE RELATIONSHIP OF CERTAIN ASPECTS

OF METABOLIC LEVEL TO HIGH OXYGEN POISONING IN RATS

by

Milton Sharp Grossman

(A.B., Harvard University, 1947)

submitted in partial fulfilment of the requirements for the degree of

Master of Arts

1948

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

TODAY STATEMENT

CHACE ROWERS OF THE STATE OF

STATE OF A PROPERTY OF A PROPERTY OF A PARTY OF A PARTY

A P & P OO.

. To

cutted the section for the degree of

SARI

1948 Gr

Approved by

First Reader . . . Semuth E. Veurrel

Professor of Physiology

Second Reader . . Brenton R. Luly .

Professor of Biology

pevoregiv

Professor of Physicalogy

Professor of Stology

# ACKNOWLEDGMENTS

I wish to express my particular appreciation and gratitude to Dr. Kenneth E. Penrod for his many help-ful suggestions and constant assistance.

To Dr. Albert H. Hegnauer I am indebted for his generous advice and criticism.

The sympathetic understanding and encouragement freely given by the late Dr. Hans O. Haterius were a source of inspiration through the past year of research on this problem.

I am deeply grateful to Miss Eleanor L. Gray for her aid in the organization and preparation of this manuscript.

My sincere thanks are offered to Miss Rose Yee and Miss Jean Flynn for their technical assistance.

5 to 10

#### ACIDIOWLED CHIEF A

I wish to express my particular appreciation and gratifude to Dr. Nemneth E. Penrod for his many help-ful suggestions and constant assistance.

To Dr. Albert H. Hegnauer I am indebted for his generous advice and oriticism.

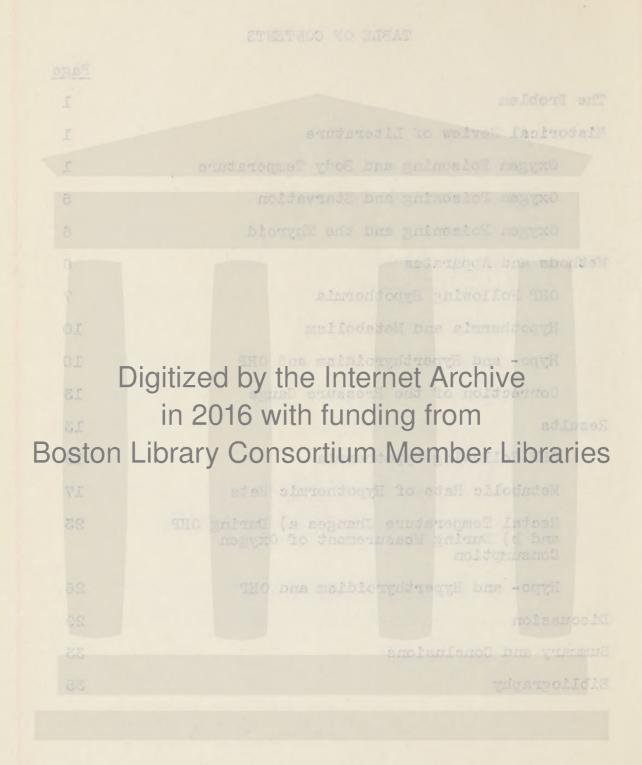
The sympathetic understanding and encouragement freely given by the late Dr. Hans O. Haterius were a source of inspiration through the past year of research on this problem.

I am deeply grateful to Miss Heaner L. Gray for her aid in the organization and preparation of this manuscript.

My sincere thanks are offered to Miss Rose Yee and Miss Jean Flynn for their technical assistance.

### TABLE OF CONTENTS

	Page
The Problem	1
Historical Review of Literature	1
Oxygen Poisoning and Body Temperature	1
Oxygen Poisoning and Starvation	5
Oxygen Poisoning and the Thyroid	6
Methods and Apparatus	6
OHP Following Hypothermia	7
Hypothermia and Metabolism	10
Hypo- and Hyperthyroidism and OHP	10
Correction of the Pressure Gauge	13
Results	13
OHP Following Hypothermia	13
Metabolic Rate of Hypothermic Rats	17
Rectal Temperature Changes a) During OHP and b) During Measurement of Oxygen Consumption	23
Hypo- and Hyperthyroidism and OHP	26
Discussion	29
Summary and Conclusions	33
Bibliography	35



# LIST OF TABLES

Table		Page
I	Calibration of the Pressure Gauge to the Nearest 0.5 psi	14
II	Survivals of 181 Rats Exposed to 5.2 Atmospheres Oxygen Pressure for One Hour	15
III	Survivals of 141 Rats Exposed to 5.8 Atmospheres Oxygen Pressure for One Hour	15
IA	Effects of Rectal Temperature Upon the Survival of Rats Exposed to 5.2 and 5.8 Atmospheres Oxygen Pressure	16
V	Metabolic Rate: Average Oxygen Consumption in Milligrams of Oxygen per 100 Grams Body Weight of Rats at the Several Rectal Temp- eratures at One Atmosphere Pressure	19
AI	Rise or Fall of Rectal Temperature of Rats a) Surviving OHP and b) During Metabolism Measurements	25
VII	Effect of Propylthiouracil and of Desiccated Thyroid on a) Survival of Rats to OHP (5.5 Atmospheres) and b) on Oxygen Consumption at Tank Temperatures of 25° to 28°C	27

#### EDET OF TARTES

Calibration of the Pressure Sauge to the Mearest 0.5 psi	b.E
Survivale of 181 Tats Exposed to 5.2 Atmospheres Oxygen Pressure for One Hour	
Survivals of 141 Bats Exposed to 5.8 Atmospheres Oxygen Pressure for One Hour	
Effects of Rectal Temperature Upon the Survival of Eats Exposed to 5.2 and 5.8 Atmospheres Oxygen Pressure	
Metabolic Hate: Average Oxygen Consumption in Militgrams of Oxygen per 100 Grams Body Weight of Eats at the Several Hectal Temperatures at One Atmosphere Pressure	61
Rise or Fall of Rectal Temperature of Rats a) Surviving OHF and b) Furing Metabolism Measurements	
Effect of Propylthioursell and of Desiccated Thyroid on a) Survival of Asta to OHP (5.5 Atmospheres) and b) on Oxygen Consumption at Tank Temperatures of 25° to 28°C	

#### LIST OF FIGURES

Figure		Page
1	ApparatusPressure Tank	9
2	Apparatus for Measuring Basal Metabolic Rate	11
3	Per Cent Survival of Cooled and Control Animals Exposed to 5.2 and 5.8 Atmospheres OHP Pressure	18
4	Comparison of Control and Hypothermic Rats With Respect to (a) Average Oxygen Consump- tion at One Atmosphere and (b) Per Cent Survival of Rats Exposed to 5.2 Atmospheres OHP Pressure	21
5	Oxygen Consumption Over a Period of One Hour and 45 Minutes of Control and Hypo- thermic Rats	22
6	Correlation Between Per Cent Survival and Oxygen Consumption of Control and Hypo-thermic Rats	24
7	Correlation Between Per Cent Survival and Oxygen Consumption of Hypo-, Hyperthyroid, and Control Rats	28

#### SERUPIT TO TRIE

		Figure
	Apparatus Fressure Tank	
	Per Sent Survival of Cooled and Control Animals Exposed to 5.2 and 5.8 Atmospheres OHP Pressure	
TS	Comparison of Control and Hypothermic Rats With Tespect to (a) Average Oxygen Consumption at One Atmosphere and (b) Per Cent Survival of Pats Exposed to 5.2 Atmospheres OHP Pressure	
	Oxygen Consumption Over a Period of One Hour and 45 Minutes of Control and Hypo- thermic Rats	
	Correlation Setween Per Cent Survivel and Oxygen Consumption of Control and Hypo-thermic Rate	
	Correlation Retween Fer Cent Survival and Oxygen Consumption of Hyporthyrold, and Control Rate	

#### THE PROBLEM

This series of experiments was performed in an attempt to clarify the relationship of metabolic levels to the survival of rats subjected to high tensions of oxygen (greater than one atmosphere). Different metabolic levels were induced by hypothermia, and by drugs that produce hypo- and hyperthyroid states. Oxygen consumptions at the various metabolic levels were determined in order to compare the oxygen consumption of the rats in each group to the number of survivals after exposure to oxygen at high pressures (hereinafter referred to as OHP). Since oxygen consumption is an index of the amount of cellular metabolism, it was felt that such a comparison would elucidate the role of cellular metabolism in poisoning by OHP.

#### HISTORICAL REVIEW OF LITERATURE

# A. Oxygen Poisoning and Body Temperature.

Priestly in 1775, shortly after having isolated oxygen (dephlogisticated air as he called it), first recognized that oxygen could have a noxious effect on the human body. Indeed he wrote,

though pure dephlogisticated air might be useful as a medicine, it might not be so proper for us in the usual healthy state of the body: for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast . . .

#### THE PROBLEM

This series of experiments was performed in an attempt to clarify the relationship of metabolic levels to the survival of rats subjected to high tensions of oxygen (greater than one stmosphere). Different metabolic levels were induced by hypothermia, and by drugs that produce hypo- and hyperthyroid states. Oxygen consumptions at the various metabolic levels were determined in order to compare the oxygen consumption of the rats in each group to the number of survivals after exposure to oxygen at high pressures (hereinafter referred to as one). Since oxygen consumption is an index of the amount of cellular metabolism, it was felt that such a comparison would colocidate the role of cellular metabolism in poisoning by OHF.

# HISTORICAL REVIEW OF LITERATURE

# A. Oxygen Poisoning and Body Temperature.

Priestly in 1775, shortly after having isolated oxygen (dephlogisticated air as he called it), first recognized that oxygen could have a noxious effect on the human body. Indeed he wrote,

though pure dephlogisticated air might be useful as a medicine, it might not be so proper for us in the usual healthy state of the body: for, as a candle burns out much faster in dephlogisticated than in common air, so we might, as may be said, live out too fast . . .

One hundred years later, Paul Bert (1878) presented extensive evidence demonstrating that animals can actually be "poisoned" by air at increased pressures (that is, greater than one atmosphere) and that this poisoning is due to the tension (partial pressure) of oxygen within the air, rather than the effect of pressure per se. Bert felt that one of the most important points of this research was the observation that "the inner temperature" (body temperature of the animal) "drops in all cases rapidly and considerably" when an animal is poisoned by high tensions of oxygen. He attributed this body temperature fall to "a diminution of intensity of chemical acts which produce the animal heat"; in other words, a decreased consumption of oxygen, and decreased production of carbonic acid and urea. The body temperature fall was of the order of 10 to 15 degrees Centigrade for all of the animals he studied (rats, mice, sparrows, and dogs), (Pressure range three to eight atmospheres OHP).

Bert's experiments on rats were done in the pressure range of three to seven atmospheres of oxygen, and between three and twelve atmospheres of air. He found that rats upon exposure to three and one-fourth atmospheres of ordinary air pressure (20% oxygen) for two and one-half hours showed no sign of oxygen poisoning and little (1°C) or no drop in rectal temperature. Whereas, in super-oxygenated air (60% oxygen) at the same pressure and for the same length of time, the rats showed definite signs of oxygen poisoning (convulsions, etc.)

sive evidence demonstrating that enimals can actually be "poisoned" by air at increased prossures (that is, greater than effect of pressure per se. Bert felt that one of the most iminner temperature" (body temperature of the enimal) "drops in benoziog at fantne ne medw "ylderebienco bne ylbiger acces ile by high tensions of oxygen. He attributed this body temperaproduce the animal heat"; in other words, a decreased consumeures. The body temperature fall was of the order of 10 to 15 .ajar) beibuja en slamina ent lo ila voi ebargitneo secreta mice, sparrows, and dogs), (Pressure range three to atmospheres OHF).

Bert's experiments on rats were done in the pressure range of three to seven atmospheres of oxygen, and between three and twelve atmospheres of air. He found that rate upon exposure to three and one-fourth atmospheres of ordinary air pressure (20% oxygen) for two and one-half hours showed no sign of oxygen potseming and little (100) or no drop in ractal temperature. Thereas, in super-oxygenated air (60% oxygen) at the same pressure and for the same length of time, the rate showed definite signs of oxygen poisoning (convalsions, etc.)

and had a rectal temperature fall of six to seven degrees.

This was considered proof that the rats were being poisoned by the partial pressure of oxygen in the air rather than by the pressure itself. The carbon dioxide content was the same in both cases.

Another experiment was designed to demonstrate the effect of the partial pressure of oxygen in a different manner. Two rats were used. One was exposed to 12 atmospheres of ordinary air (20% oxygen) for three hours, while the other rat was exposed to two and one-third atmospheres of 100% oxygen for three hours. Both rats died soon after decompression, having had only a four degree drop in rectal temperature. This experiment was repeated on large numbers of sparrows and dogs, with exactly the same results. Note that it required five times the amount of compressed air as 100% oxygen to poison the animals, but that the tensions of oxygen (the partial pressures) were the same in each case.

Hill and MacLeod (1903 a,b,c,) found a drop in body temperature and diminished carbon dioxide output and oxygen absorption in rats, mice, and young rabbits exposed to OHP (two to ten atmospheres) and proposed that these metabolic changes are a sign of poisoning by oxygen.

Thompson (1889) reported a decrease in body temperature of 14°C in monkeys, pigeons, guinea pigs, and dogs exposed to OHP (4.2 atmospheres for one hour). However, an alligator exposed to OHP for the same time and pressure showed no signs of

and had a rectal temperature fall of six to seven degrees.

This was considered proof that the rats were being poisoned by the partial pressure of oxygen in the air rather than by the pressure itself. The carbon dioxide content was the same in both cases.

Another experiment was designed to demonstrate the effect of the partial pressure of exygen in a different manner. Two rats were used. One was exposed to 12 atmospheres of ordinary air (20% oxygen) for three hours, while the other rat was exposed to two and one-third atmospheres of 100% oxygen for three hours. Both rats died soon after decompression, having had only a four degree drop in rectal temperature. This experiment was repeated on large numbers of sparrows and dogs, with exactly the same results. Note that it required five times the amount of compressed air as 100% oxygen to poison the animals, but that the tensions of oxygen (the partial pressures) were the same in each case.

Hill and MacLeod (1903 a,b,c,) found a drop in body temperature and diminished carbon dioxide output and oxygen absorption in rats, wice, and young rabbits exposed to OHP (two to ten atmospheres) and proposed that these metabolic changes are a sign of poisoning by oxygen.

Thompson (1889) reported a decrease in body temperature of 14°C in mankeys, pigeons, guines pigs, and dogs exposed to OHP (4.2 atmospheres for one hour). However, an alligator exposed to OHP for the same time and pressure showed no signs of

oxygen poisoning, and its body temperature increased from 51.25 to 75°F (environmental temperature 66°C).

Cleveland (1925) found that frogs were more resistant to OHP than warm-blooded animals.

Almeida (1934,a), Dionessow, et. al. (1934), and Hederer and Andre (1940) found a similar decrease in body temperature in several different warm-blooded animals.

One cannot use body temperature as an index of metabolic changes in animals exposed to OHP without reservation and care. Hill and MacLeod (1903,c) pointed out that the "increased thermal conductivity" of a compressed gas contributes to the lowering of the body temperature of animals exposed to OHP.

Campbell (1937,a) stressed the importance of environmental temperature upon survival of animals exposed to OHP. An environmental temperature of 24°C seemed to protect the rats upon exposure to OHP (six atmospheres for 30 minutes) in comparison with animals exposed to a 33°C environmental temperature under the same experimental conditions. At 24°C, 31 out of 58 rats, or 53.5% survived. At 33°C, three out of 39 rats or 7.7% survived. He assumed that the lower environmental temperature lowered the body temperature. He further assumed that the higher environmental temperature prevented the body temperature from falling when the rats were exposed to OHP. Therefore, he concluded that lowered body temperatures protected animals upon exposure to OHP. Yet he presented no experimental evidence to support his assumptions. It must be pointed out that a 33°C

oxygen poisoning, and its body temperature increased from 51.25 to 75°F (environmental temperature 66°C).

Cleveland (1925) found that frogs were more resistant to OHP than warm-blooded animals.

'Almeida (1934,a), Diomessow, et. al. (1934), and Hederer and Andre (1940) found a similar decrease in body temperature in several different warm-blooded animals.

One cannot use body temperature as an index of metabolic changes in animals exposed to OHF without reservation and care. Hill and MacLeod (1905,c) pointed out that the "increased thermal conductivity" of a compressed gas contributes to the lowering of the body temperature of animals exposed to OHF.

temperature upon survival of animals exposed to OFP. An emvironmental temperature of 24°C seemed to protect the rats upon exposure to OHP (six atmospheres for 30 minutes) in comparison with animals exposed to a 35°C environmental temperature under the same experimental conditions. At 24°C, 31 out of 58 rats, or 55.5% survived. At 35°C, three out of 59 rats or 7.7% survived. He assumed that the lower environmental temperature lowered the body temperature. He further assumed that the higher environmental temperature prevented the body temperature from falling when the rats were exposed to OHP. Therefore, he concluded that lowered body temperatures protected animals upon exposure to OHP. Yet he presented no experimental evidence to support his assumptions. It must be pointed out that a 33°C

environmental temperature cannot be construed as a normal temperature. It is well known that healthy rats succumb readily to such high environmental temperatures without subjecting them to any experimental procedures. This has been our experience also.

The effect of environmental temperature in the poisoning of insects by OHP was demonstrated by Williams and Beecher (1944) in experiments on Drosophila. At 34.2°C and five atmospheres of oxygen, the rate of poisoning was eight times as rapid as at the temperature 14.4°C.

It does not seem that any well substantiated conclusions can be drawn from the previous literature about the effect of environmental temperature in poisoning of warm-blooded animals by OHP.

# B. Oxygen Poisoning and Starvation.

Almeida (1934,a) showed that starvation lessens mortality of animals exposed to OHP, the theory being that starvation decreases the metabolism and therefore increases the resistance of animals to OHP. This effect of starvation has been confirmed by Campbell (1937,a,b) and Hederer and Andre (1940).

<sup>1.</sup> This statement has been confirmed by Mr. Everett Aubry, Breeder of the Charles River Laboratories, Boston. It is the experience of that Laboratory that 31.5°C environmental temperature is the upper limit that rats can tolerate without serious damage to their health. Above this temperature, heat exhaustion, stunted growth, loss of weight, and death are not uncommon.

environmental temperature cannot be construed as a normal temperature. It is well known that healthy rats succumb readily to such high environmental temperatures without subjecting them to any experimental procedures. I This has been our experience also.

The effect of environmental temperature in the poisoning of insects by OHP was demonstrated by Williams and Beecher (1944) in experiments on Drosophila. At 54.2°C and rive atmospheres of oxygen, the rate of poisoning was eight times as rapid as at the temperature 14.4°C.

It does not seem that any well substantiated conclusions can be drawn from the previous literature about the effect of environmental temperature in poisoning of warm-blooded animals by OHP.

# B. Oxygen Poisoning and Starvation.

Almeida (1934,a) showed that starvation lessens mortality of enimals exposed to OHP, the theory being that starvation decreases the metabolism and therefore increases the resistance of animals to OHP. This effect of starvation has been confirmed by Campbell (1957,a,b) and Hederer and Andre (1940).

<sup>1.</sup> This statement has been confirmed by Mr. Everett Aubry, Breeder of the Charles River Laboratories, Boston. It is the experience of that Laboratory that 51.500 environmental temperature is the upper limit that rate can tolerate without serious damage to their health. Above this temperature, heat exhaustion, stunted growth, loss of weight, and death are not uncommon.

#### C. Oxygen Poisoning and the Thyroid.

campbell (1937,b) administered thyroxin (0.4 mgm.) to rats and found that this enhanced oxygen poisoning (exposure to six atmospheres of oxygen for 30 minutes at 24°C environmental temperature). Whereas removal of the thyroid gland of rats increased the resistance to oxygen poisoning even when the environmental temperature was raised to 33°C. At 33°C environmental temperature and six atmospheres of oxygen for 30 minutes, he had previously found a 7.7% survival (Campbell, 1937,a). Of six thyroidectomized rats exposed to the same pressure and environmental temperature for the same length of time, all survived and showed no signs of oxygen poisoning. On the basis of these experiments, Campbell stated, "... oxygen poisoning is due to acceleration and increase of the usual oxidative processes in the nerve centers; ... the thyroid gland plays an important part in this toxic action.".

#### METHODS AND APPARATUS

In order to determine more accurately the significance of body temperature change and its relationship to metabolism in OHP, it was decided to investigate the effect upon survival of cooling rats to rectal temperatures of 20°, 25°, and 30°C.

Secondly, it seemed pertinent to reinvestigate the effects of hypo- and hyperthyroidism by slightly different techniques than those employed by Campbell (1937,b) so that a
comparison could be made of the results of two different

# C. Oxygen Polsoning and the Thyroid.

Campbell (1957,b) administered thyroxin (0.6 mgn.)
to rate and found that this enhanced oxygen poisoning (exposure
to six atmospheres of oxygen for 50 minutes at 24°C environmental temperature). Whereas removal of the thyroid gland of
rate increased the realistance to oxygen poisoning even when
the environmental temperature was raised to 35°C. At 55°C
environmental temperature and aix atmospheres of oxygen for
50 minutes, he had previously found a 7.7% survival (Campbell,
1957.s). Of aix ingredictionized rate exposed to the same
pressure and environmental temperature for the same length of
time, all survived and showed no signs of oxygen poisoning.
On the basis of these experiments, Campbell stated. "...
oxygen poisoning is due to acceleration and increase of the
usual oxidative processes in the nerve centers; ... the

#### METHODS AND APPARTUS

In order to determine more accurately the significance of body temperature change and its relationship to metabolism in OHP, it was decided to investigate the effect upon survival of cooling rats to rectal temperatures of  $20^\circ$ ,  $25^\circ$ , and  $30^\circ$ c.

Secondly, it seemed pertinent to reinvestigate the effects of hypo- and hyperthyroidism by slightly different techniques than those employed by Campbell (1957,b) so that a comparison could be made of the results of two different methods of altering metabolism.

#### A. OHP Following Hypothermia.

- 1. Male albino rats of the Wistar strain, purchased from the Charles River Breeding Laboratories, Boston, were used. (Average weight 200 grams; range 150 to 300 grams)
- 2. All animals were starved twenty-four hours and were weighed before being used in the experiments.
- 3. All of the animals used (both the experimental and control) were plainly marked by cuts in the ear and/or cresyl violet dots on the back of the neck.
- 4. Experimental rats were placed in individual boxes and their rectal temperatures taken by insertion of a thermometer previously brought to within one degree of the estimated rectal temperature.
- 5. The experimental rats were then placed in ice water up to the neck until their rectal temperature (which was checked every five minutes) reached the desired level. They were then quickly removed from the water and dried with a dry towel. Then they were immediately placed in the pressure tank.
- 6. Control rats (37°C rectal temperature) were exposed to OHP simultaneously with the hypothermic rats. In some cases the controls were immersed in 37°C water for the same period of time as the immersion of the hypothermic rats in the colder water. In the majority of cases the controls were merely dipped in water and dried to the same extent as the hypothermic rats. In still other cases the controls were not

#### A. OHP Following Hypothermia.

- 1. Male albino rate of the Wister strain, purchased from the Charles River Breeding Laboratories, Boston, were used. (Average weight 200 grams; range 150 to 300 grams)
  - 2. All enimals were starved twenty-four hours and were weighed before being used in the experiments.
- S. All of the animals used (both the experimental and control) were plainly marked by cuts in the ear and/or cresyl violet dots on the back of the neck.
  - 4. Experimental rate were placed in individual boxes and their rectal temperatures taken by insertion of a thermometer previously brought to within one degree of the estimated rectal temperature.
- 5. The experimental rats were then placed in ice water up to the neck until their rectal temperature (which was checked every five minutes) reached the desired level. They were then quickly removed from the water and dried with a dry towel. Then they were immediately placed in the pressure tank.
- 6. Control rats (37°C rectal temperature) were exposed to OHP simultaneously with the hypothermic rats. In some cases the controls were immersed in 37°C water for the same period of time as the immersion of the hypothermic rats in the colder water. In the majority of cases the controls were merely dipped in water and dried to the same extent as the hypothermic rats. In still other cases the controls were not

immersed at all. No significantly different results were obtained in any of the three groups of control animals upon exposure to OHP.

- 7. The six to ten rats (experimental and control) were placed in the pressure tank (see Figure 1) immediately after they were dried, and the pressure increased gradually over a 15-minute period to 60 pounds per square inch (hereinafter referred to as psi) gauge pressure (five atmospheres) or to 68 psi gauge pressure (5.5 atmospheres) with 99.8% pure medical oxygen from an oxygen cylinder.
- 8. The tank temperature was kept constant at 20° or 25°C by controlling the room temperature.
- 9. A continuous flow of oxygen was maintained by adjustment of the blow-off valve.
- 10. Compression at peak pressure was maintained for one hour.
- 11. The analysis of air taken from the tank at different intervals during compression did not show any detectable
  amounts of carbon dioxide.
- 12. Decompression was gradual over a period of 30 minutes (approximately two pounds per minute).
- 13. As soon as the rats were removed from the pressure tank, their rectal temperatures were recorded.
- 14. Arbitrarily, any animal that was alive 10 days after exposure was considered a survivor.

inmoraed at all. We significantly different headles were obtained in any of the taree groups of control animals upon exposure to OHP.

- 7. The six to ten rats (experimental and control) were placed in the pressure tank (see Figure 1) immediately after they were dried, and the pressure increased gradually over a 15-minute period to 60 pounds per square inch (herein after referred to as psi) gauge pressure (five atmospheres) or to 68 psi gauge pressure (5.5 atmospheres) with 99.8% pure medical oxygen from an oxygen cylinder.
- 8. The tank temperature was kept constant at 20° or 25° d by controlling the room temperature.
- 9. A continuous flow of oxygen was maintained by ad-
  - . 10. Compression at peak pressure was maintained for one hour,
- 11. The analysis of air taken from the tank at different intervals during compression did not show any detectable amounts of carbon dioxide.
  - 12. Decompression was gradual over a period of 30 minutes (approximately two pounds per minute).
- 13. As soon as the rate were removed from the pressure tenk, their rectal temperatures were recorded.
  - 14. Arbitrarily, any animal that was alive 10 days after exposure was considered a survivor.

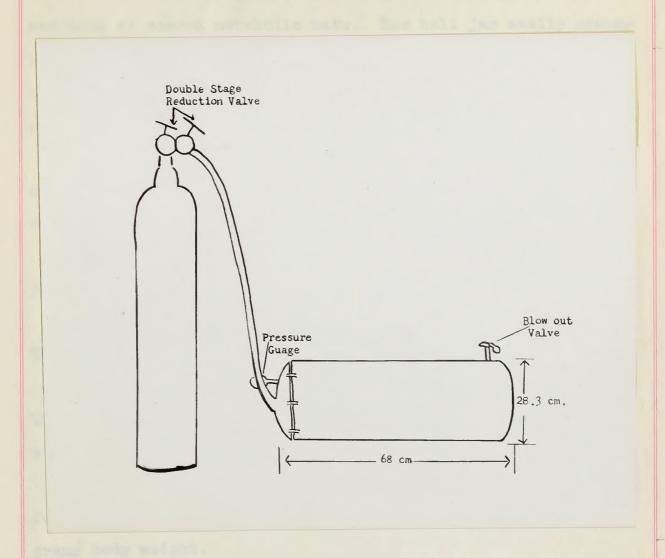


Figure 1

Apparatus--Pressure Tank

Figure 1

Must surseff--smousqua

#### B. Hypothermia and Metabolism.

- l. The apparatus shown diagrammatically in Figure 2 was used to record metabolic rate. The bell jar easily accommodated five rats. Soda lime for carbon dioxide absorption was placed both in the bell jar and in the spirometer and replaced at frequent intervals.
- 2. The spirometer was filled with oxygen. The oxygen consumption of rats cooled to 20°, 25°, and 30°C, and control rats (37°C) was measured.
- 3. Five rats cooled to a specific temperature were placed in the bell jar for a given experiment.
- 4. Rats starved for 24 hours were used in all cases. The animals were weighed immediately before using.
- 5. The bell jar, sealed with mercury, was opened to the spirometer. The apparatus was allowed to come to a constant temperature before the recording started.
- 6. Oxygen consumption was measured for one hour and forty-five minutes and recorded as milligrams oxygen per 100 grams body weight.
- 7. Upon removal from the bell jar, the rectal temperatures were recorded.

# C. Hypo- and Hyperthyroidism and OHP.

1. 25 rats were fed a diet of 0.03% 6-n-propylthiouracil mixed in the Rockland Farms Rat Diet ( New City)

# B. Hypothermia and Metaboliam.

- 1. The apparatus shown diagrammatically in Figure 2 was used to record metabolic rate. The bell jar easily accommodated five rats. Soda lime for carbon dioxide absorption was placed both in the bell jar and in the spirometer and replaced at frequent intervals.
  - 2. The spirometer was filled with oxygen. The oxygen consumption of rats cooled to  $20^{\circ}$ ,  $25^{\circ}$ , and  $50^{\circ}$ G, and control rats  $(37^{\circ}\text{G})$  was measured.
  - 3. Five rats cooled to a specific temperature were placed in the bell jar for a given experiment.
- 4. Rats starved for 24 hours were used in all cases.
  The animals were weighed immediately before using.
- 5. The bell jar, sealed with mercury, was opened to the spirometer. The apperatus was allowed to come to a constant temperature before the recording started.
- 6. Oxygen consumption was measured for one hour and forty-five minutes and recorded as milligrams oxygen per 100 grams body weight.
- 7. Upon removal from the bell jar, the rectal temperatures were recorded.

# C. Hypo- and Hyperthyroidism and OHP.

1. 25 rats were fed a diet of 0.03% 6-n-propyl-thiouracil mixed in the Rockland Farms Rat Diet (New City)

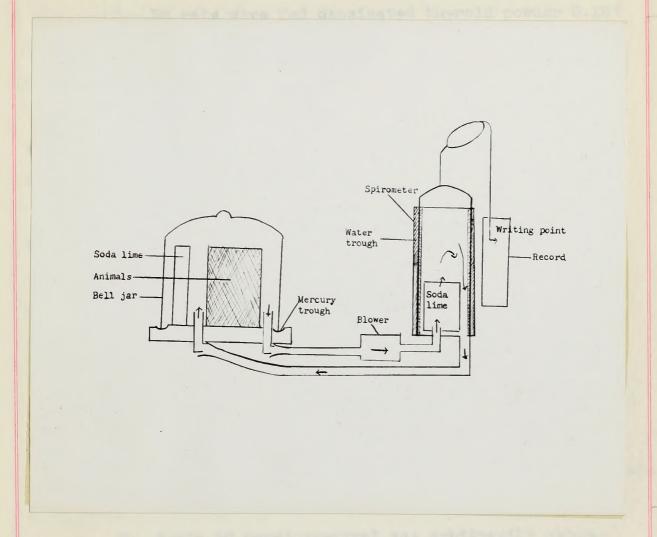


Figure 2

Apparatus for Measuring Basal Metabolic Rate

Figure 2

Apparatus for Heasuring Basal Metabolic Rate

New York) for 22 days. 1,2

- 2. 25 rats were fed the normal Rockland Farms Rat Diet which was the stock diet in our colony.
- 3. 25 rats were fed dessicated thyroid powder 0.12% in the diet for six to eight days. One rat died on the fifth day from unknown causes.
- 4. Oxygen consumptions were determined as before on each group of rats (five at a time) just before placing them in the pressure tank. Rats starved for 24 hours were used.
- 5. Rectal temperatures were recorded before placing the rats in the pressure tank.
- 6. Two or three rats from each group (equal numbers from each group) were placed in the pressure tank for each experiment.
- 7. Compression was as before (A, 6 to 14) but to 64 psi maintained for one hour. Tank temperature ranged from 25° to 28°C.
- 8. Rectal temperatures, taken as previously described, were recorded immediately following removal from the tank.
  - 9. Again 10 days' survival was arbitrarily chosen.

<sup>1.</sup> Dosages suggested by Dr. E. B. Astwood of the New England Medical Center, Boston (personal communication).

<sup>2.</sup> Propylthiouracil through the courtesy of Lederle Laboratories.

- New York) for 22 days. 1,2
- 2. 25 rats were fed the normal Reckland Farms Rat Diet which was the stock diet in our colony.
- 3. So rate were fed descioated thyroid powder 0.18; in the diet for six to eight days. One rat died on the fifth day from unknown causes.
  - 4. Oxygen consumptions were determined as before on each group of rats (five at a time) just before placing them in the pressure tank. Hats starved for 24 hours were used.
  - 5. Rectal temperatures were recorded before placing the rate in the pressure tank.
  - 6. Two or three rats from each group (equal numbers from each group) were placed in the pressure tank for each experiment.
  - 7. Compression was as before (A, 6 to 14) but to 64 psi maintained for one hour. Tank temperature ranged from  $25^{\circ}$  to  $28^{\circ}$  c.
- B. Rectal temperatures, taken as previously described, were recorded immediately following removal from the tenk.
  - 9. Again 10 days' survivel was arbitrarily chosen.

<sup>1.</sup> Dosages suggested by Dr. E. Astwood of the New England Medical Center, Hoston (personal communication).

<sup>2.</sup> Propylthiouracil through the courtesy of Lederle

#### D. Correction of the Pressure Gauge.

It has been stated that the animals in these experiments were compressed to 60, 64, or 68 psi gauge pressure.

After completion of the entire series of experiments, our gauge was tested against a standard mercury gauge. The results of this test are listed in Table I. It may be seen that when the rats were subjected to a reading of 60 psi on our gauge, they were actually compressed to 61.5 psi or 5.2 atmospheres. Similarly, compression to 68 psi on our gauge was actually compression to 70.5 psi or 5.8 atmospheres, and compression to 64 psi was actually 65.5 psi or 5.5 atmospheres pressure. It may be noted that varying the environmental temperatures between 20° and 30°C did not change the gauge readings.

#### RESULTS

## A. OHP Following Hypothermia.

The effects of cooling upon the survival rate of rats exposed to OHP can be seen in Tables II, III, and IV. Table II represents 181 rats exposed to 5.2 atmospheres oxygen pressure. The rats were treated in the following ways: a) rats cooled to rectal temperatures of 20°, 25°, and 30°C; b) tank temperature 20° and 25°C; and c) control rats. Table III represents 141 rats exposed to 5.8 atmospheres of oxygen pressure treated in the same ways as the rats in Table II.

### O. Correction of the Pressure Cauce.

It has been stated that the enimals in these experiments were compressed to 60, 64, or 65 pel gauge pressure.

After completion of the entire series of experiments, our
gauge was tested against a standard mercury gauge. The results of this test are listed in Table I. It may be seen that
when the rate were subjected to a reading of 60 psi on our
gauge, they were actually compressed to 61.5 psi or 5.2 atmospheres. Similarly, compression to 68 psi on our gauge was
actually compression to 70.5 psi or 5.8 atmospheres, and compressure. It may be noted that verying the environmental
pressure. It may be noted that verying the environmental
readings.

#### RESULTS

## A. OH Pollowing Hypothermia.

The effects of gooling upon the survival rate of rate exposed to OHP can be seen in Tables II, III, and IV. Table II represents 181 rate exposed to 5.2 atmospheres oxygen pressure. The rate were treated in the following ways: a) rate cooled to rectal temperatures of 20°, 25°, and 50°8; b) tank temperature 20° and 25°C; and c) control rate. Table III represents 141 rate exposed to 5.8 atmospheres of oxygen pressure treated in the same ways as the rate in Table II.

TABLE I
Calibration of the Pressure Gauge
to the Nearest 0.5 psi

Standard Mercury Gauge Readings	Our Gauge Readings
50.0 psi	48.0 psi
55.0 psi	53.5 psi
60.0 psi	58.5 psi
65.0 psi	63.6 psi
70.0 psi	67.5 psi
75.0 psi	72.0 psi
80.0 psi	76.0 psi

Note: Environmental temperature was varied between 20°C and 30°C without changing the gauge readings.

TABLE I
Calibration of the Pressure Gauge
to the Meanest O.5 psi

Readings	Our Cauge	Standard Mercury Gauge: Readings
isq	48.0	50.0 psi
psi	53.5	55.0 psi
lag	58.5	i 1aq 0.00
pai	65.6	1ag 0.38
psi	67.5	70.0 psi
ing	0.27	75.0 pst
lag	76.0	: leg 0.0S

Note: Mavironmental temperature was varied between 20°C and 30°C without changing the gauge readings.

TABLE II

Survivals of 181 Rats
Exposed to 5.2 Atmospheres Oxygen Pressure for One Hour

Rectal Temp.	Tank Temp.		ors Per Cent
: 20°C	20°C	9 of 10	90 %
25°C	20°c	3 of 12	25 %
30°C	20°C	9 of 12	75 %
37°c	20°C	18 of 36	69.2%
20°C	25°C	32 of 40	80 %
25°C	25°C	18 of 38	47.4%
30°C	25°C	5 of 13	38.4%
37°c	25 <sup>°</sup> C	17 of 30	56.4%

TABLE III

Survivals of 141 Rats
Exposed to 5.8 Atmospheres Oxygen Pressure for One Hour

Rectal Temp.	Tank Temp.	Surviv Numbers	ors Per Cent
20°C	20°C	1 of 16	6.25%
25°C	20°C	3 of 12	25 %
30°C	20°C	3 of 12	25 %
37°C	20°C	5 of 23	21.8 %
20°C	25°C	3 of 19	15.8 %
25°C	25°C	3 of 23	13 %
30°C	25°C	1 of 8	12.5 %
37°C	25°C	5 of 27	18.5 %

#### THE HE

Survivals of 181 Hats of Leaders Constant on French Pour

y or s : Per Cent	ivrus:	Tank Temp.	Rectal Temp.
00 :	01 to 0 :	2000	
: 25 %	8 of 13	o <sup>o</sup> os	25°c
75 %	81 20 8	p°os	
19.28	18 of 36	o°os	57°c
à 08 :	52 of 40	2500	
: 47.45	18 of 58	es°o	25°c
58.4%	5 of 13	25°c	30 <sup>9</sup> 08
56.45	17 of 30	25°c	20,45

TIL HARAT

Survivals of 141 Rats
Exposed to 5.8 Atmospheres Caygen Pressure for One Hour

vors	Lv n u 2 Numbers	Tank Temp.	Rectal Temp.
: 6.25¢	al to I	0000	0008
: 25 %	S of 12	0000	2500
25 %	S of 18	2000	50 <sup>0</sup> 0
% 8.T8 ;	5 of 25	5°0S	57°C
15,8 %		25°o :	20°0S
: 15 %	3 of 23	988	25°c
: 12.5 %	1 of 8	25°c	30°0
: 18.5 %	5 of 27	25°0	37°c

TABLE IV

### Effects of Rectal Temperature

Upon the Survival of Rats

Exposed to 5.2 and 5.8 Atmospheres Oxygen Pressure

Rectal Temp.	Tank Pressure	Survi	ors
		Numbers	Per Cent
20°C	5.2 atmos.	41 of 50	82 %
	5.8 atmos.	4 of 35	11 %
25°C	5.2 atmos.	21 of 50	42 %
	5.8 atmos.	6 of 35	17 %
30°C	5.2 atmos.	14 of 25	56 %
	5.8 atmos.	4 of 20	20 %
37°C	5.2 atmos. 5.8 atmos.	35 of 56 10 of 50	62.4%

TABLE IV

# Effects of Rectal Temperature

#### Upon the Survival of Fata

Exposed to 5.2 and 5.8 Atmospheres Cxygen Pressure

arov	lvas 8	Tank Pressure	Rectal Temp.
Per Cent			
g ti		.somia S.3 .somia S.3	20°c
A SA		5.2 atmos. : 5.8 atmos. :	5°63
56 X 20 Z 20 Z		5.2 atmos. : 5.8 atmos. :	30°0
88.45 20 \$	35 of 56 10 of 50	5.2 atmos. : 5.8 atmos. :	0,048

Table IV was constructed to summarize the effects of the various levels of body temperature on survival when exposed to OHP. Figure 3 is a graph of the data in Table IV. The striking difference in survivals between 5.2 atmospheres OHP and 5.8 atmospheres is noteworthy.

In constructing Table IV we did not take environmental (tank) temperature into account, for the following reason:

Although some workers have reported that environmental temperature has a marked effect upon the survivals of warm-blooded animals exposed to OHP (see Historical Review), we have not found a significant difference in the survivals of rats at 20°C and 25°C environmental (tank) temperature. The probability of there being such a difference was found by the chi square technique to be of the order of 0.79, or considerably below the accepted level of significance.

## B-1. Metabolic Rate of Hypothermic Rats.

The metabolic rate of rats cooled to 20°C, 25°C, 30°C and of 37°C controls is recorded in Table V. Several different formulae have been reported for finding the surface area of a rat. Yet, no one formula or constant has been generally accepted. Therefore, to avoid confusion we have followed the method of Carr and Krantz (described in The Rat in Laboratory Investigation, 1942) and have expressed metabolic rate in milligrams of oxygen consumed per 100 grams body weight. The oxygen consumption has been measured for one hour and fortyfive minutes (which is the total time the rats are in the tank

Table IV was constructed to summarize the effects of the various levels of body temperature on survival when exposed to OHP. Figure 5 is a graph of the date in Table IV. The strikting difference in survivals between 5.2 atmospheres OHP and 5.8 atmospheres is noteworthy.

In constructing Table IV we ild not take environmental (tank) temperature into account, for the following reason:

Although some workers have reported that environmental temporature has a marked effect upon the survivals of warm-blooded enimals exposed to OHP (see Historical Review), we have not found a significant difference in the survivals of rate at 20°0 and 25°0 environmental (tank) temperature. The probability of there being such a difference was found by the chi square technique to be of the order of 0.79, or considerably below the accepted level of significance.

# Bal. Metabolic Rate of Brookingeric Rate.

The metabolic rate of rate couled to 20°C, 25°C, 30°C and of 37°C controls is recorded in Table V. Several cifferent formulae have been reported for finding the surface area of a rat. Yet, no one formula or constant has been generally accepted. Therefore, to avoid confusion we have followed the method of Cerr and Brants (described in The Rat in Laboratory Investigation, 1942) and have expressed metabolic rate in milligrams of oxygen consumed per 100 green body weight. The oxygen consumption has been measured for one hour and forty-

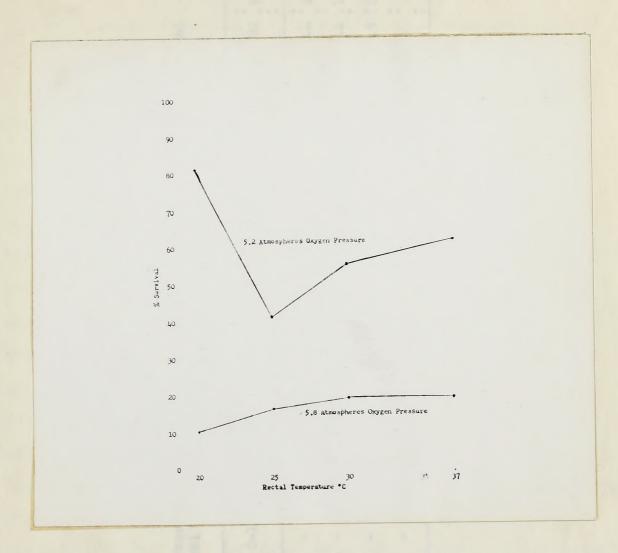


Figure 3

Per Cent Survival
of Cooled and Control Animals
Exposed to 5.2 and 5.8 Atmospheres OHP Pressure

Figure 3

Per Cent Survival
of Cooled and Control Animals
Exposed to 5.2 and 5.8 Atmospheres OHP Pressure

TABLE V

Metabolic Rate: Average 02 Consumption in mgm. 02/100 gms. Body Weight of Rats at the Several Rectal Temperatures at One Atmosphere Pressure.

	••••	• •	•••	
90-10	124.9	113.0	144.5	
75-90	109.4 124.9	160.4 113.0	:143.5 :144.5	
Avg. for 1 hr. under 75-90 90-105 compression	0.97	180.8	165.5	1.9.1
60-75	9.96	190.1	: 167	1.49.1
8 45-60	7.06	186.7	162.3	1.9.1
Minutes 30-45	66.7	182.8	162.7	149.1
15-30	50	163.6	170	1.49.1
0-15	t		i	1
No. of Rats : 0-15	25	25	25	25
Rectal temp. No. of at start Rats	20.02	25°C	30.08	37°C

LTBTE A

edf da edel lo dagiel ybod .ang COI\\C .mgm bi noligmmetol co egement steded officials

	3. JANE .	0. CIL.	154.9	30-708
1	C.EME.	T00.1	T-60T.	00-37·
Train	168.8	18048	76.0	Tebour Tot L
-	**	·	. 6.30	4-00 4-00
£	181	. 190		* *
I.RAI	162.3	7.081	30.7	
f. Q.L	Tes-1.	188.8	7.00	Bedunia.
	9 8	0	, ,,	
. 749.	. T.30	. Te3.		08-51
į.		1		0.75
Q.	25	9	05	No. off
3hod	30°C	2000	50.0	. qmet Istoeff trafa ta

under positive pressures). However, we are primarily interested in the oxygen consumption during the one hour that the rats would be exposed to the highest tensions of oxygen. Consequently, column 8 of Table V is devoted to the average oxygen consumption for the period of 15 to 75 minutes for each of the four categories. Attention is called to the difference in average oxygen consumption between 20°C, 25°C, 30°C, and 37°C rectal temperature. It must be made clear that this analysis has been carried on at one atmosphere. It is most difficult to carry on accurate oxygen consumption studies at greater than one atmosphere. It has been impossible to do it with the experimental setup described in this paper. The oxygen consumption for the first 15 minutes of the analysis could not be obtained, because of the changes in temperature within the apparatus during the time temperature equilibrium was being established, and because an adequate amount of time had to be allowed for absorption of carbon dioxide by the soda lime. It has been our experience that this takes a maximum of 10 minutes. Figure 4 is a graph of the data in column 8 of Table V. and a graph of the per cent survival of animals exposed to 5.2 atmospheres pressure (from the data in Table IV). The similarity in the two curves may be readily seen.

The oxygen consumption over the recorded one hour and 30 minutes is represented in Figure 5. The oxygen consumption for  $20^{\circ}$ C rectal temperature seems to be approximately a straight line function and is the lowest of the four categories.

under positive preseures). However, we are primarily interestwould be exposed to the highest tensions of oxygen. Consequently, column 8 of Table V is devoted to the average oxygen consumption for the period of 15 to 75 minutes for each of the Tour categories. Attention is called to the difference in average oxygen consumption between 20°C. 25°C. 50°C. and 50°C rectal temperature. It must be made clear that this analysis distribution at tI .erengeomia eno ja no betriso meed and to carry on accurate oxygen consumption studies at greater than one atmosphere. It has been impossible to do it with the experimental setup described in this paper. The exygen consumption for the first 15 minutes of the analysis could not be obtained, because of the changes in temperature within the apparatus during the time temperature equilibrium was being established, and because an adequate amount of time had to be allowed for absorption of carbon dioxide by the soda lime. It has been our experience that this takes a maximum of 10 minutes. Figure 4 is a graph of the data in column 8 of Table V, and a ereph of the per cent survivel of animals exposed to 5.2 atmospheres pressure (from the date in Table IV). The similarity in the two curves may be readily seen.

The oxygen consumption over the recorded one hour and 30 minutes is represented in Figure 5. The oxygen consumption for 200 c rectal temperature seems to be approximately a straight line function and is the lowest of the four categories.



Figure 4

Comparison of Control and Hypothermic Rats With Respect to a) Average Oxygen Consumption at One Atmosphere and b) Per Cent Survival of Rats Exposed to 5.2 Atmospheres OHP Pressure

## A sumill

Comparison of Control and Hypothereds Sate
With Respect to a) average Coggen Consumption at One
Atmosphere and b) For Cont Servivel of Rate Deposed
to 6.2 Atmosphere GEF Freezure

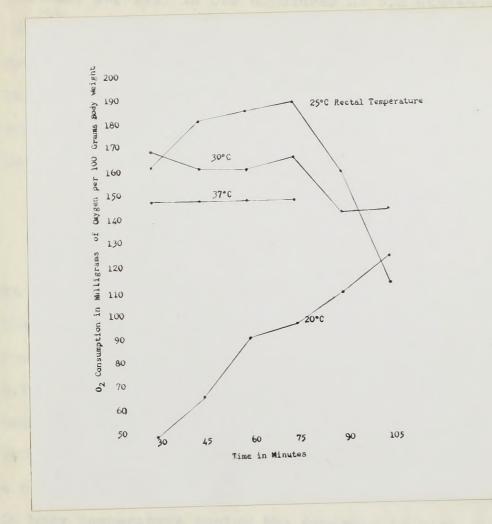


Figure 5

Oxygen Consumption
Over a Period of One Hour and 45 Minutes
of Control and Hypothermic Rats

Mgare 5

Over a Period of One How and 15 Mantes of Control and Hypotherale Rats Five and two-tenths atmospheres, 25°C rectal temperature is the level at which the rats are most susceptible to OHP and the oxygen consumption is greatest. The relationship between per cent survival in OHP exposures at 5.2 atmospheres (as described in Table IV) and average oxygen consumption (as described in column 8 of Table V) is shown in Figure 6. This indicates clearly the inverse relationship between oxygen consumption at one atmosphere and per cent survival at OHP, the correlation coefficient being -0.963.

# B-2. Rectal Temperature Changes a) During OHP and b) During Measurement of Oxygen Consumption.

In line with the observations of Bert and others, we found a fall in rectal temperature of control rats during their exposure to positive pressures of oxygen. The average rectal temperature fall of control rats during exposure to 5.2 and 5.8 atmospheres of pressure at tank (environmental) temperatures of 20° and 25°C are shown in the last column of Table VI. Those rats that began exposure to high oxygen with a rectal temperature reduced below normal tended toward a rise in body temperature during the exposure to high oxygen. The rise was inversely correlated with the rectal temperature at the beginning of the exposure. That is, those rats cooled to 20°C showed a greater temperature rise during the one hour and forty-five minutes exposure than did those rats cooled to 25°C. This rise in rectal temperature was much more pronounced in those rats exposed to 5.2 atmospheres pressure than in those

Five and two-tenting atmospheres, 25°C rectal temporature is the level at which the rate are most susceptible to ORP and the oxygen consusation is greatest. The relationship ontween per cent survival in ORP exposures at 5.2 sincepheres (as described in Table IV) and average oxygen consumption (as described in column 8 of Table V) is shown in Figure 6. This indicates clearly the inverse relationship between oxygen consumption at one atmosphere and per cent survival at OHP, the sumption at one atmosphere and per cent survival at OHP, the

8-2. Rectal Temperature Changes a) During OHP and b) Luring Measurement of Oxygen Consumption.

we found a fall in rectal temperature of control rate during their exposure to positive pressures of oxygen. The average rectal temperature fall of control rate during exposure to 5.2 and 5.8 atmospheres of pressure at temic (environmental) temperatures of 20° and 25°0 are shown in the last column of Table VI. Those rate that began exposure to high oxygen with a rectal temperature reduced below normal tended toward a rise in body temperature during the exposure to high oxygen. The rise was inversely correlated with the rectal temperature at the occinning of the exposure. That the beginning of the exposure. That is, those rate cooled to and forty-five minutes exposure than did those rate cooled to and forty-five minutes exposure than did those rate cooled to and forty-five minutes exposure than did those rate cooled to and forty-five minutes exposure than did those rate cooled to in those rate exposure than in those rate axposure than in those rate exposure than in those rate axposure than in those rate axposure than in those rate exposed to 5.2 atmospheres pressure than in those

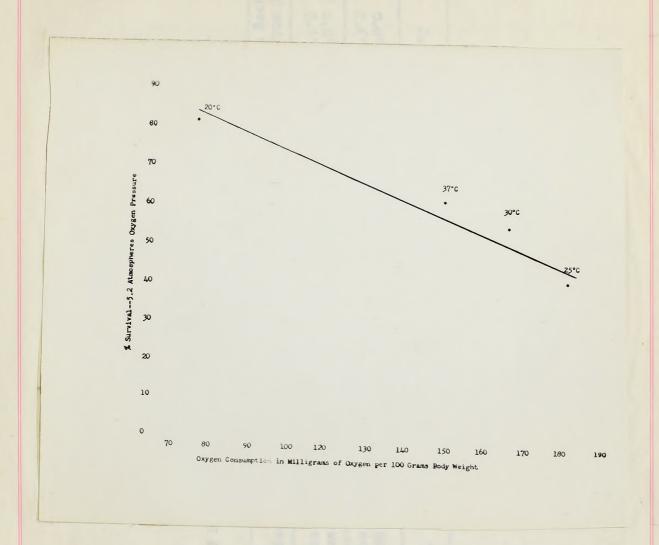


Figure 6

Correlation Between Per Cent Survival and Oxygen Consumption of Control and Hypothermic Rats

Figure 6

Correlation Setween Per Cent Survival and any Consumption of Control and Hypothermic Rate

TABLE VI

b) During Rise or Fall of Rectal Temperature of Rats a) Surviving OHP, and Metabolism Measurements.

• •

Tank Temp. Tank Press. 20°C 5.2 atmos. 20°C 5.8 atmos.		20°C 25°C 30°C + 4.6°C (-1.5 to +2.5) + 2.6°C + 1.65°C 0°C (-2.0 to +3.2)	30°C -1.5 to +2.5) -2.0 to +3.2)	Temp. from 37°C -2.9°C -7.0°C
5.2 atmos. 5.8 atmos.	+11.6°C + 7.2°C	+ 6.7°C +	+3.8°C +1.3°C	-2.3°C
25 to 28°C · latmos.	+11.01°C	+11.4°C; +	+7.6°C	2.0

			0	
			THE BUT	
			PE MICH	
		000		
	in in	2.0.0		
	D.0.6.	78		
			自自	
			Lemp.	
	** **			
		20 60	12	
		in in		
			*	
		00	30°C	
	(2) 00		1 777 1-1	
-	J.3°0	0.1	100	
	74			
			1 00	
			1	
		0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.		
			层	
		0.00		
477.40			Des Dico	
	00 -3			
			50 .	
	2-0		S. dans.	
		++		
	0.00			
	0 0			
	0.0	00		
-	-16	30 %		
			1	
	in in	00 00		
(0)				
	見見			1
	1 00 TE	00.00		
		NIM		
	* * * * *			
			10	
			· que	
		00		
		00		
		20°C		
			1 1	

exposed to 5.8 atmospheres.

It would appear that the return to normal body temperature is somewhat delayed by the exposure to high oxygen pressures since, with one exception, the rise at one atmosphere was considerably greater over the same period of time than was the rise during OHP exposure.

#### C. Hypo- and Hyperthyroidism and OHP.

The results of the thyroid experiments are listed in Table VII. It should be noted that this series of experiments was carried out at 5.5 atmospheres oxygen pressure for the reason that previous experimentation indicated that this pressure would give approximately 50% survival of control rats if they were exposed for the same length of time as the previous experiments (one hour). From the Table it is apparent that the propylthiouracil markedly depressed oxygen consumption, since the average was reduced to 95 milligrams-per cent, whereas the control group had an oxygen consumption of 149 milligramsper cent. The hyperthyroids showed an average oxygen consumption of 182 milligrams-per cent. Figure 7 shows the relation between the average oxygen consumption and the per cent survival when exposed to OHP in each of the three groups. correlation between oxygen consumption and per cent survival is quite high, namely -0.985.

exposed to 5.8 atmospheres.

It would appear that the return to normal body temperature is somewhat delayed by the exposure to high oxygen pressures since, with one exception, the rise at one atmosphere was considerably greater over the same period of time than was the rise during OHP exposure.

# O. Hypor and Hyperthyroidism and OHP.

The results of the thyroid experiments are listed in Table VII. It should be noted that this series of experiments was carried out at 5.5 atmospheres oxygen pressure for the reason that previous experimentation indicated that this pressure would give approximately 50% survival of control rats if they were exposed for the same length of time as the previous experiments (one hour). From the Table it is apparent that the propylthioursell markedly depressed oxygen consumption, since the average was reduced to 95 milligrams-per cent, whereas the control group had an oxygen consumption of 149 milligrams-per cent. The hyperthyroids showed an average oxygen consumption of 182 milligrams-per cent. Figure 7 shows the relation between the average oxygen consumption and the per cent survival when exposed to OFF in each of the three groups. The correlation between oxygen consumption and per cent survival squite high, namely -0.985.

TABLE VII

Effect of Propylthiouracil and of Desiccated Thyroid on a) Survival of Rats to OHP (5.5 atmos.) and b) on O<sub>2</sub> Consumption at Tank Temperatures of 25° to 28°C.

	•				Control Regular Diet		.Hyperthyroid 'Receiving Desiccated 'Thyroid in Diet		
		No	o. of	s. 1 atmos.  02 Consump- s tion mg/100 gms. body wt.	No. of Survivors	. 02 Consum-	No. of Survivors	. 02 Consump	
#1	• • • •	4	of 5	76 mg 0 <sub>2</sub>	4 of 5	178.5mg 0 <sub>2</sub>	2 of 5	234 mg 0 <sub>2</sub>	
2	•	5	of 5	82.5	2 of 5	122	2 of 5	171	
3	• • •	4	of 5	:102	:2 of 5	: 126	: 1 of 4	120	
4		4	of 5	124	2 of 5	161.8	2 of 5	210	
5	•	3	of 5	93	4 of 5	157.2	0 of 5	175	
7			of 25 80%	Average = 96 mg 0 <sub>2</sub>		Average = 149.0 mg 0 <sub>2</sub>	7 of 24 = 29%	Average = 182.0 mg 0 <sub>2</sub>	

#### LIV ALSAT

Effect of Propolithiouseil and of Desiceated Toroid on a) Survival of Mats to ORP (5.5 atmos.) and b) on O2 arrival of Mats to ORP (5.5 atmos.) and b) on O2 Consumption at Tank Temperatures of 25° to 28°C.

: bedecolee	Hyperthyrol Receiving D Thyrold in		Control Regular Di			
letonsump- tion mg/100 gms. body	No. of Encylvars	. Og Consum-; tion mg/loc	no. of	enusari -godanumg/100 fon mg/100 gms. body	No. of Survivors	*
234 mg 02	2 30 5	178.5mg 02		76 mg 02	6 20 A	. It
. ILI	2 30 5	122		82.5	5 of 5	; s
120 :	1 20 1	: 126		102	Lot 5	3
: 010	2 30 5	8.191	E 20 S	124	4 08 5	4:
175	. 2 10 0	137.2	£ 36 1	93	3 02 5	5 :
Average = 182.0	(a-	. = 149.0	14 of 25 = 56%	: 96 =	20 of 25 = 80%	

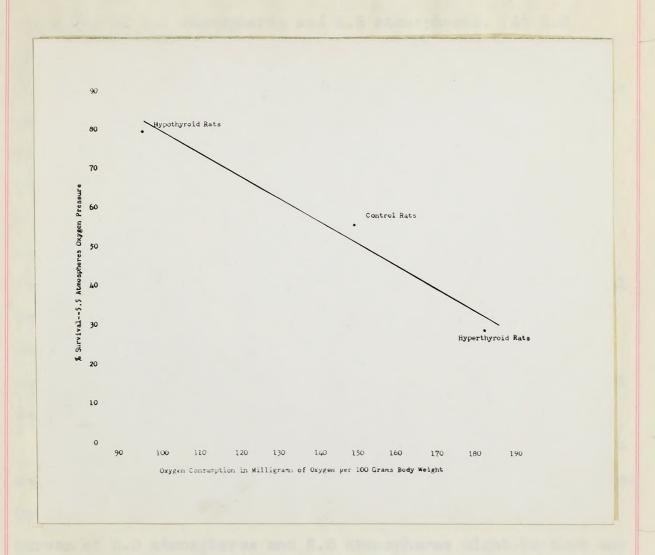


Figure 7

Oxygen Consumption of Hypo-, Hyperthyroid, and Control Rats

Pinne 7.

Correlation Sotwoon Per Cent Survival and Outgen Consumption of Hyporthyroid, and Control Rate

#### DISCUSSION

The data obtained reveal a striking difference between poisoning at 5.2 atmospheres and 5.8 atmospheres. At 5.2 atmospheres definite protection is afforded animals cooled to 20°C rectal temperature before exposure to OHP. It is significant that 20°C rectal temperature is just 4°C higher than the average lethal temperature for rats (The Rat in Laboratory Investigation, 1942). It is further significant that rats cooled to 20°C had the lowest oxygen consumption. At 20°C rectal temperature all of the rats were deeply narcotized. Very little narcosis was observed in rats cooled to 25°C rectal temperature and no narcosis observed in rats cooled to 30°C rectal temperature. Cooling to temperatures higher than 20°C seemed to enhance poisoning. Rats cooled to 25°C were the most susceptible to OHP and had the highest oxygen consumption.

As can be seen from Figure 3, there is no significant difference in survivals amongst the four groups at 5.8 atmospheres.
One possible explanation of the sharp difference between the
curves of 5.2 atmospheres and 5.8 atmospheres might be that any
protective or deleterious effects of cooling to the three
rectal temperatures is masked by the tremendous susceptibility
of rats to OHP poisoning at 5.8 atmospheres for one hour.

It would seem from our data that the pressure that would kill 50% of the control animals (the lethal dose 50%, hereinafter referred to as  $LD_{50}$ ) must be somewhere between 5.2 atmospheres and 5.8 atmospheres. For this reason 5.5 atmospheres of

#### MOTESTORIA

The data obtained reveal a striking difference between poisoning at 5.2 atmospheres and 5.8 atmospheres. At 5.2 atmospheres definite protection is afforded animals cooled to 20°C rectal temperature before exposure to OHP. It is significant that 20°C rectal temperature is just 4°C higher than the captage lethal temperature for rate (The Rat in Imporatory Investigation, 1948). It is further algnificant that rate cooled to 20°C had the lowest expanded consumption. At 20°S rectal rectal temperature all of the rate were deeply narcotized. Very little narcosis was observed in rate cooled to 25°C rectal temperature and no narcosis observed in rate cooled to 30°C rectal rectal temperature. Cooling to temperatures higher than 20°C rectal seemed to enhance poisoning. Rate cooled to 25°C were the most seemed to enhance poisoning. Rate cooled to 25°C were the most succeptible to OHP and had the highest oxygen consumption.

As can be seen from Figure 5, there is no significant difference in survivals amongst the four groups at 5.8 atmospheres.

One possible explanation of the sharp difference between the
curves of 5.2 atmospheres and 5.8 atmospheres might be that any
protective or deleterious effects of cooling to the three
rectal temperatures is masked by the tremendous susceptibility
of rats to 0HP poisoning at 5.8 atmospheres for one hour.

It would seem from our data that the pressure that would kill 50% of the control animals (the lethal dose 50%, herein-after referred to as LD50) must be somewhere between 5.2 atmospheres of pheres and 5.8 atmospheres of

oxygen pressure was chosen for the thyroid experiments. A limited number of rats did indicate that this pressure must be very close to the theoretical LD<sub>50</sub>. From these data it seems justifiable to conclude that, for our strain and age rats, the toxicity of oxygen increases sharply at pressures above five atmospheres. Likewise, Stadie (1945,b) found eight atmospheres of oxygen pressure for 30 minutes to be 90 to 100% lethal for rats.

It has been pointed out that, in our experience, there appears to be no significant difference in survivals of rats exposed to OHP in environmental temperatures of 20 and 25°C.

Bert and others (see Historical Review) found a decrease in body temperature of 10 to  $15^{\circ}$ C (rectal temperature) in rats and other animals exposed to OHP. We have found the drop of body temperature in the control rats exposed to OHP ranges from 3 to  $7^{\circ}$ C (average 3.8°C). In no case did we find a drop of more than  $7^{\circ}$ C.

The fact that there is a sharp difference between one atmosphere and 5.2 or 5.8 atmospheres in the amount of temperature rise in cooled rats and in the amount of fall of body
temperature of control rats during exposure (see Table VI),
tends to indicate that the metabolic processes of the body are
intimately involved in oxygen poisoning. Nevertheless, we can
not state at this time the significance, if any, of this
temperature change.

oxygen pressure was chosen for the thyroid experiments. A limited number of rats did indicate that this pressure must be very close to the theoretical LD50. From these data it seems justifiable to conclude that, for our strain and age rats, the toxicity of oxygen increases sharply at pressures above five atmospheres. Likewise, Stadie (1945,h) found eight atmospheres of oxygen pressure for 30 minutes to be 90 to 100% lethal for rats.

It has been pointed out that, in our experience, there appears to be no significant difference in survivals of rate expensed to OHP in environmental temperatures of 20 and 25°C.

Bert and others (see Mistorical Review) found a decresse in body temperature of 10 to 15°C (rectal temperature) in rate and other animals exposed to OHP. We have found the drop of body temperature in the control rate exposed to OHP ranges from 5 to 7°C (average 3.8°C). In no case aid we rind a drop of more than 7°C.

The fact that there is a sharp difference between one atmosphere and 5.2 or 5.8 atmospheres in the amount of temperature rise in cooled rate and in the amount of fall of body
temperature of control rate during exposure (see Table VI),
tends to indicate that the metabolic processes of the body are
intimately involved in oxygen poisoning. Hevertheless, we can
not state at this time the significance, if any, of this
temperature change.

Our work on the thyroid has confirmed the work of Campbell (1937,b). Decreased thyroid activity, caused by administration of propylthiouracil and indicated by a decreased oxygen consumption, definitely protects animals from the toxic effects of oxygen at increased pressures. Increased thyroid activity, caused by the administration of desiccated thyroid powder and indicated by an increased oxygen consumption, enhances the toxic effects of OHP.

The most significant outcome of these experiments, however, is the high inverse correlation between per cent survival and oxygen consumption in both the hypothermia series and the thyroid series. This relationship might be expected on the grounds that a sluggish metabolic system would be less susceptible to mass action stimulus of high concentrations of oxygen. These data do not appear to confirm the belief of Stadie (1945,a,b,c) that enzyme systems are inhibited, inasmuch as enzymatic inhibition should be independent of the rate of oxygen consumption in the animal exposed to OHP. Bean's hypothesis (1945) of the accumulation of carbon dioxide in the tissues due to the inability of oxygen saturated hemoglobin to transport the carbon dioxide away from the tissues is not untenable in the light of these data. However, critical evaluation of this point cannot be made from this data.

The exact mechanism or mechanisms whereby high oxygen tensions evoke a toxic reaction to the living animal is not yet apparent. It is significant that by and large those animals

Our work on the thyroid has emiliased the work of Campbell (1837,b). Decreased thyroid activity, caused by administration of propylchiomesal and indicated by a decreased oxygen consumption, definitely protects animals from the toxic effects of oxygen at incremed pressures. Increased thyroid sctivity, caused by the administration of desiceated thyroid powder and indicated by an increased oxygen consumption, admines the toxic effects of Offe.

The most significant oniceds of these experiments, however, is the high inverse correlation between per cent murvival and oxygen consumption in both the hypothermia series and the thyroid series. This relationship might be expected on the grounds that a singular metabolic cystem would be less susceptible to mass action stimulus of high concentrations of oxygen. These data do not appear to confirm the belief of stanishing data do not appear to confirm the belief of stanishing and the engine systems are inhibited, insense as engaged to the rate of oxygen consumption in the animal exposed to OHP. Bean's hypothesis to the inability of extrem saturated hemoglobin to transport to the inability of extrem saturated hemoglobin to transport to the light of these way from the tissues is not retearable in the light of these data. However, critical evaluation of this

The exact mechanism or mechanisms whereby high oxygen tenafons evoke a toxic reaction to the living animal is not yet apparent. It is significant that by and large those animals

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS

which succumb to exposure to high oxygen do so during or immediately after the exposure. Very rarely does an animal who survives the first four hours following exposure later die.

In some instances, however, localized paralysis indicative of central nervous system lesions can be observed, but it is rare for these animals to survive for very long periods.

The difference between animals following exposure to OHP is quite striking. Some animals seem to be completely unharmed by their experience and immediately go about preening themselves. Very infrequently do these animals die. Their rectal temperature rises to normal within a few hours after removal from the tank, regardless of their rectal temperature at the start of the experiment. Other animals are obviously in distress when removed from the tank. They have convulsive seizures; they exhibit gasping movements. Almost universally, they have considerable nasal and oral exudate of a watery nature. Oftentimes, nasal hemorrhages have been observed. The rats are wet, even if they have not been dipped in water before the start of the experiment. As a rule, these animals die within a few hours, or at most, a few days. Rewarming or artificial respiration is to no avail. One finds that immediately following death a state of extension rigidity exists. This differs from rigor mortis in that it (the rigidity) comes on in a matter of minutes as compared with the one to two hours post morten characteristic of rigor mortis in the rat.

It would appear that the toxicity of high pressures of

which succumb to exposure to high oxygen do so during or immediately after the exposure. Very rarely does an animal who survives the first four hours following exposure later die. In some instances, however, localized paralysis indicative of cantral nervous system lesions can be observed, but it is rare for these animals to survive for very long periods.

is quite striking. Some animals seem to be completely unharmed salves. Very infrequently do these animals die. Their rectal from the tank, regardless of their rectal temperature at the .etb mt vlauotvdo ens elamine rento .inemireque ent lo frate tress when removed from the tank. They have convulsive seizures; they exhibit gasping movements. Almost universally, they have considerable nasal and oral exidate of a watery neture. Oftentimen, nasal hemorrhages have heen observed. The rate are wet, even if they have not been dipmed in water die within a few hours, or at most, a few days. Hewarming or -ibeant jed respiration is to no sysil. One finds that immedi-

To servesery dgid to vileity out tadt reeque bluow il

oxygen is an acute rather than a chronic phenomenon and is intimately related to the normal metabolic processes of the body. A slowing down of these metabolic processes apparently independent of the means, appears to offer some protection to the organism against the effects of the high oxygen pressures.

#### SUMMARY AND CONCLUSIONS

- 1. A striking difference in per cent survival of rats exposed to 5.2 atmospheres and to 5.8 atmospheres OHP for one hour is described, indicating that poisoning by increased oxygen tensions does not proceed as a simple arithmetic progression.
- 2. Results of a series of 131 animals indicate that for rats exposed to OHP for one hour, 5.5 atmospheres is the approximate pressure required for 50% survival.
- 3. Moderate changes in environmental temperature have no significant effect upon survival rates of rats exposed to increased oxygen tensions.
- 4. A decrease in rectal temperature of only 3-7°C (average 3.8°C) in rats exposed to OHP is reported. The discrepancy between these results and those of previous workers is discussed.
- 5. Normal rats show a fall in rectal temperature when exposed to OHP. Rats whose body temperature have been lowered by immersion in ice water show a slower rate of recovery at increased pressures than at one atmosphere.

oxygen is an acute rather than a chronic phenomenon and in intimately related to the normal metabolic processes of the body. A slowing down of these metabolic processes apparently independent of the means, appears to offer some protection to the organism against the effects of the high oxygen pressures.

# SUMMARY AND CONCLUSIONS

- 1. A striking difference in per cent survival of rate exposed to 5.2 atmospheres and to 5.3 atmospheres one hour is described, indicating that poisoning by increased ony—gen tensions does not proceed as a simple arithmetic progression.
- 2. Results of a series of 131 animals indicate that for rats exposed to OHP for one hour, 5.5 atmospheres is the approximate pressure required for 50% survival.
  - 5. Moderate changes in environmental temperature have no significant effect upon survival rates of rate exposed to increased exygen tensions.
  - 4. A decrease in rectal temperature of only 5-70 (average 5.800) in rate exposed to OHP is reported. The discrepancy between these results and those of previous workers is discussed.
  - 5. Normal rate show a fall in rectal temperature when exposed to OHP. Rate whose body temperature have been lowered by inversion in ice water show a slower rate of recovery at increased pressures than at one atmosphere.

- 6. The rate of oxygen consumption of rats at one atmosphere pressure shows a high negative correlation with per cent survival at increased oxygen tensions.
- a) Rats which are cooled to a rectal temperature of 20°C show a decreased consumption of oxygen and an increased resistance to OHP in comparison with normal control rats at 37°C.
- b) Rats cooled to 25°C and 30°C show increased consumption of oxygen and decreased resistance to OHP.
- c) Rats treated with propylthiouracil (hypothyroid rats) show a decreased consumption of oxygen and an increased resistance to OHP.
- d) Rats treated with desiccated thyroid powder show an increased consumption of oxygen and a decreased resistance to OHP.

- 5. The rate of oxygen consumption of rate at one atmosphore pressure shows a high negative correlation with per cont
  survival at increased oxygen tensions.
  - 20°C show a decreased consumption of oxygen and an increased restance to OHP in comparison with normal control rate at 57°C.
  - b) hats cooled to 2500 and 3000 show increased consumption of oxygon and decreased resistance to OHP.
  - o) Hats treated with propylthicuraell (hypothyreid rats) show a decreased consumption of oxygen and an increased resistance to CHF.
  - d) Hate treated with desiceated thyroid powder show an increased consumption of oxygen and a decreased resistance to OHP.

#### BIBLIOGRAPHY

- Almeida, A. O. de, "Recherches sur l'action Toxique Des Hautes Pressions D'oxygene", Compt. rend. Soc. de Biol., Paris 116, 1225, 1934a
- Almeida, A. O. de, "Traitement et Guerison Par l'oxygene Du Cancer Experimental Des Rats", Compt. rend. Soc. de Biol., Paris 116, 1228, 1934b
- Bean, John W., "Effects of Oxygen at Increased Pressure", Physiol. Rev., 25:1-147, 1945
- Bert, Paul, "La Pression Barometrique", 1878, as translated by Hitchcock, M. A., and F. A. Hitchcock, College Book Company, Columbus, Ohio, 1943 (quotations from pp. 714, 743)
- Campbell, J. A., "Body Temperature and Oxygen Poisoning", J. of Physiol., 89: 17P, 1937a
- Campbell, J. A., "Oxygen Poisoning and the Thyroid Gland", J. of Physiol., 90: 91P, 1937b
- Cleveland, L. R., Toxicity of Oxygen for Protozoa," Biol. Bull., 48:455, 1925
- Dionessow, S. M., B. D. Krawtschinsky and S. I. Prikladowizki, Fiziol. Zhur., 17:1004, 1934, as quoted by J. W. Bean, "Effects of Oxygen at Increased Pressure", Physiol. Rev., 25:1-147, 1945
- Griffith, J. Q., Jr. and E. J. Farris, The Rat in Laboratory
  Investigation, Philadelphia, J. B. Lippincott Company,
  1942
- Hederer, C. and L. Andre, "De l'intoxication par les hautes pressions d'oxygene", Bull. Acad. de med., Paris (3rd series) 123:294, 1940
- Hill, L. and J. J. R. MacLeod, "The Influence of Compressed Air and Oxygen on the Gases of the Blood", J. of Physiol., 29:382, 1903a
- Hill, L. and J. J. R. MacLeod, "The Influence of Compressed Air in the Respiratory Exchange", J. of Physiol., 29:492, 1903b

# YHAARDO IJIB IE

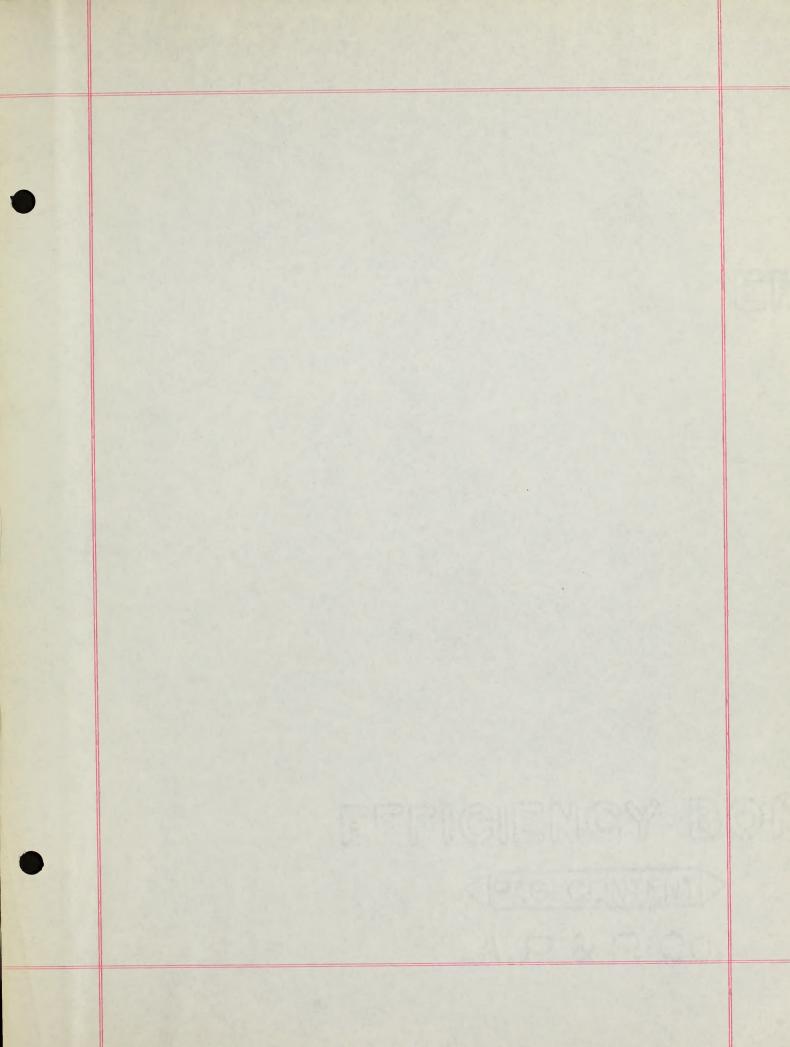
- Almeida, A. O. de. "Recherches sur l'action Toxique Des Hautes Pressions D'oxygene", Compt. rend. Soc. de Biol., Paris 116, 1885, 1984a
- Almoids, A. D. de, "Traitoment et Guerison Par l'oxygone Du Cancer Experimental Des Rats", Compt. rend. Soc. de Biol.. Paris 116, 1228, 1934b
  - Bean, John W., "Effects of Caygon at Increased Pressure", Physiol. Rev., 25:1-147, 1945
  - Bert, Paul, "La Fression Rarometrique", 1076, as translated by Hitchcock, M. A., and F. A. Hitchcock, College Book Company, Columbus, Ohio, 1945 (quotations from pp. 714, 743)
    - Campbell, J. A., "Body Vergerature and Oxygen Poisoning", J. of Physiol., 89: 17P, 1957a
    - Campbell, J. A., "Oxygen Polsoning and the Thyroid (land", J. of Physick., 90: 812, 1937b
      - Cleveland. I. R., Toxicity of Cxyyen for Protozoa." Biol. Bull., 48:455, 1925
  - Dionessow, S. M., B. D. Brawtschinsky and S. I. Prikladowizki, Fishel. Shur., 17:1004, 1934, as quoted by J. W. Bean, "Effects of Oxygen at Increased Pressure", Physiol. Rev., 25:1-147, 1945
    - Criffith, J. G., Jr. and E. J. Farris, The Mat in Laboratory
      Investigation, Philadelphia, J. B. Lippincott Company,
      1942
      - Hederer. C. and L. Andre. "De l'Intexication par les hautes prossions d'oxygene", Bull. Acad. de med., Paris (5rd series) 125:294, 1940
- Hill, L. and J. J. R. Hacheod, "The Influence of Compressed Air and Caygen on the Gases of the Blood", J. of Physicl., 29:582, 1905s
  - Hill, L. and J. J. R. MacLeod, "The Influence of Compressed Air in the Respiratory Exchange", J. of Physiol., 29:492, 1905b

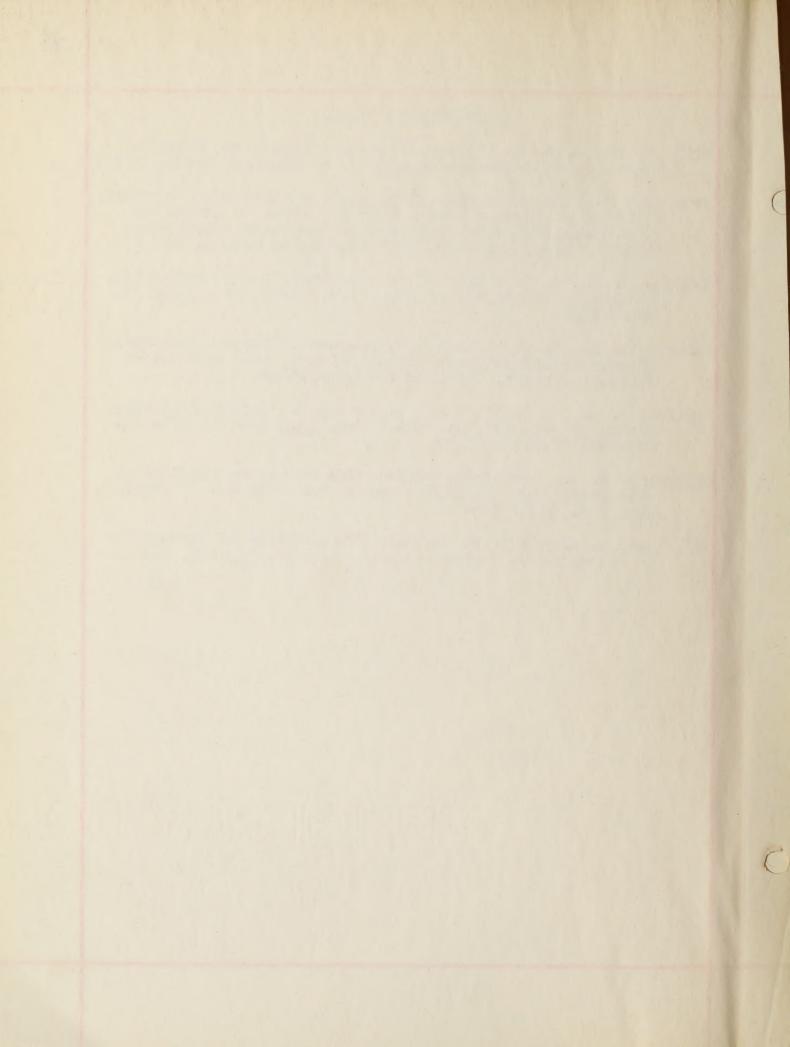
## BIBLIOGRAPHY (Cont.)

- Hill, L. and J. J. R. MacLeod, "Caisson Illness and Diver's Palsy--An Experimental Study", J. of Hygiene, 3:401, 1903c
- Priestly, J., "The Discovery of Oxygen", Alembic Club Reprints, 7, Univ. of Chicago Press, Chicago, 1906, as quoted by J. W. Bean, "Effects of Oxygen at Increased Pressure", Physiol. Rev., 25:1-147, 1945 (quotation from p. 2)
- Stadie, W. C., B. C. Riggs and H. Haugaard, "Oxygen Poisoning, Effects on Metabolism of Brain", J. Biol. Chem. 160:191-208, 1945a
- Stadie, W. C., B. C. Riggs and H. Haugaard, "Oxygen Poisoning, Effects on Metabolism of Liver, Kidney, Lung and Muscle Tissue", J. Biol. Chem. 160:209-216, 1945b
- Stadie, W. C., B. C. Riggs and H. Haugaard, "Oxygen Poisoning, Effect on Enzymes", J. Biol. Chem. 161:153-174, 175-180, 181-188, 189-196, 1945c
- Thompson, W. G., "The Therapeutic Value of Oxygen Inhalation, With Exhibition of Animals under High Pressure of Oxygen", Med. Rec. 36:1, 1889
- Williams, C. M. and H. K. Beecher, "Sensitivity of Drosophila to Poisoning by Oxygen", Am. J. Physiol. 140:566, 1944

## BIBLIOGRAPHY (Cont.)

- Hill, L. and J. J. R. MacLood, "Caisson Illness and Diver's Palsy -- An Experimental Study", J. of Hygiene, 5:401, 1905c
- Priestly, J., "The Discovery of Oxygen", Alembia Club Heprints, 7, Univ. of Chicago Pross, Chicago, 1906, as quoted by J. W. Bean, "Effects of Oxygen at Increased Pressure", Physiol. Rev., E5:1-147, 1845 (quotation from p. 2)
  - Stadle, W. C., B. C. Miggs and H. Haugsard, "Oxygen Polsoning, Effects on Metabolism of Ersin", J. Biol. Chem. 160:191-203, 1945a
  - Stadle, W. C., B. C. Riggs and H. Haugaard, "Oxygen Polsoning, Effects on Metabolism of Liver, Midney, Tung and Miscle Tissue", J. Biol. Chem. 160:200-216, 1945b
  - Stadie, W. C., B. C. Riggs and H. Haugeard, "Cxygen Polsoning, Mifect on Marymee", J. Biol. Chem. 161:155-174, 175-180, 181-188, 189-196, 1945c
- Thompson, W. G., "The Therapeutic Value of Oxygen Inhalation, With Exhibition of Actuals under High Pressure of Oxygen", Ned. Rec. 36:1, 1889
  - Williams, C. M. and H. K. Beecher, "Sensitivity of Drosophila to Polsoning by Oxygen", Am. J. Physicl. 140:585, 1944







# REDI COVER NF 58138

A Product of Wilson Jones Co.

